The Role of Hyperinsulinemia in Slipped Capital Femoral Epiphysis

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Background: Obesity in the prepuberal stage has been directly associated with slipped capital femoral epiphysis (SCFE). Serum insulin level increases in the prepuberal and adolescence stage, to a greater extent in the obese population. The main objective of this article was to analyze the relationship between insulin levels and SCFE.

Methods: A case-control study was conducted between January 2018 and April 2019. The study group was formed with patients with SCFE and the control group with patients from the pediatric obesity clinic of our hospital selected during their initial evaluation. None were being treated for obesity. Anthropometric measurements of size, weight, waist circumference, and blood pressure were taken. Body mass index (BMI) and waist-height index of all patients were calculated. According to BMI for age, they were classified as normal, overweight, or obese. Serum determinations of glucose, insulin, glycated hemoglobin, lipid profile, and complete blood count were analyzed. Insulin resistance was diagnosed with Homeostatic Model Assessment (HOMA) >3. Insulin levels >13 U/mL for girls and >17 U/mL for boys were considered as hyperinsulinemia.

Results: We studied 14 patients with SCFE and 23 in the control group. The mean age and BMI in both groups were similar. The elevation of serum insulin was significantly higher in the SCFE group ($P=0.001$) as was HOMA ($P=0.005$). Triglycerides and very-low-density lipoprotein were higher in the SCFE group ($P=0.037$ and 0.009, respectively). Glycemia, glycated hemoglobin, total cholesterol, high-density lipoprotein, low-density lipoprotein, and neutrophils showed no significant difference.

Conclusions: Patients with SCFE showed elevated levels of insulin, HOMA, triglycerides, and very-low-density lipoprotein, even higher than the control group. Our study demonstrates a significant association between abnormally high serum insulin levels and SCFE. The known effects of insulin on growth cartilage may explain the physeal mechanical insufficiency to support the abnormally high or repetitive loads in accelerated growth stages that lead to SCFE.

Level of Evidence: Level III—case-control, prognostic study.

Key Words: SCFE, slipped capital femoral epiphysis, pediatric hyperinsulinemia, pediatric obesity, hyperinsulinemia

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Slipped capital femoral epiphysis (SCFE) is an immature hip disorder characterized by anatomic disruption through the proximal femoral physis. It is believed to be the result of mechanical insufficiency of the physeal plate and is produced by the abnormally high load in a normal physis, physiological load in an abnormally weak physis, or their combination. Among the mechanical factors for abnormally high load are obesity, acetabular or femoral retroversion, coxa profunda, and increased physeal obliquity.[1,2]

Prepubescent obesity is directly associated with SCFE.[3–6] However, only in 5% to 8% of cases debilitating endocrine alterations of the physis, such as hypothyroidism, growth hormone deficiency, hypogonadism, and parathyroid hormone alterations are found.[2,7,8] This inconstancy contributes to obesity being considered a mechanical factor in the pathogenesis of SCFE. However, the increased burden on the physis due to overweight or obesity does not completely explain its association with SCFE. Children of the same age, without obesity, are exposed to high mechanical hip demands during recreational and sports activities without developing the disease. Physeal weakening during peaks of accelerated growth, associated with early growth in obese children and adolescents, is probably the main causal factor of SCFE.[9,10]

The association between obesity and SCFE is well known. The relationship between obesity and hyperinsulinemia during prepubescent and adolescent ages is also known.[10–12] Serum insulin increases in the prepubescent and adolescence stages to a greater extent in obese patients.[11,12] However, no reports have associated hyperinsulinemia and SCFE. The main objective of this article was to analyze the relationship between SCFE and hyperinsulinemia.

METHODS

A case-control study, approved by the Research Committee of our hospital, was conducted. From January 2018 to April 2019, we prospectively included patients

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between 7 and 15 years of age. Two groups were formed: the study group, comprising patients with SCFE, either before or after receiving surgical treatment and the control group, age-matched and sex-matched, comprising patients from the pediatric obesity clinic of our hospital at their initial evaluation, before receiving dietary or pharmacological treatment. The exclusion criteria were being under treatment to reduce glucose or serum insulin levels, suggestive or confirmative medical history of endocrine disease, and lacking complete laboratory studies. The parents were informed about the participation of their children in the study, and consent was obtained in each case.

We evaluated the following anthropometric parameters: height, weight, waist circumference, body mass index (BMI), waist-to-height ratio, and blood pressure (BP). All were measured with the same instrument and by the same evaluator. BP was taken with a digital wrist baumanometer. BMI, according to the World Health Organization (WHO) tables, was considered normal between the fifth and 85th percentiles, overweight between the 85th and 95th percentiles, and obesity as >95th percentile. BP was classified according to systolic pressure for height/age: normotensive <90th percentile, prehypertensive between the 90th and 95th percentiles, and hypertensive >95th percentile.[13]

From a morning blood sample, after at least 8 hours of fasting, the following were analyzed: glucose, insulin, glycated hemoglobin (HbA1c), lipid profile, and complete blood count. Blood glucose >125 mg/dL was considered diagnostic for type 2 diabetes mellitus (T2DM).[14] Serum insulin was considered high for an age when it was >13 µU/mL for girls and >17 µU/mL for boys.[11] The Homeostatic Model Assessment (HOMA) was obtained by multiplying the fasting serum glucose (mg/dL) by the serum insulin (µU/mL), divided by the constant 405. Results >3 were indicative of insulin resistance (IR).[15,16] HbA1c <5.7% was considered normal, between 5.7% and 6.4% was considered at risk for T2DM, and >6.5% was indicative of a diagnosis of T2DM.[17] Blood chemistry and the lipid profile were analyzed by chemiluminescence with the AU5800 device, Beckman Coulter, Brea, California, HbA1c was analyzed by chromatography with a VARIANT II Hemoglobin Testing System, Bio-Rad Hercules, California, insulin was analyzed using radioimmunoassay with a UniCel DxI 800 Access Immunoassay System, Beckman Coulter, Brea, California and total blood count was determined using flow cytometry on a CELL-DYN Ruby analyzer Abbott, Abbott Park, Illinois.

The demographic characteristics are expressed as the mean and range for continuous variables and for qualitative frequencies. The laboratory results are shown as mean and SD with the 95% confidence interval (CI). The comparison of the laboratory results between the 2 groups was performed with the *t* test for independent samples. For this, IBM SPSS Statistics 25 for Windows IBM Corp., Armonk, New York was used. The odds ratio (OR) was calculated as a risk estimator for dichotomous variables between groups, with a 95% CI (Epi Info, version 7.2 for Windows, Centers for Disease Control and Prevention, Atlanta, Georgia). In all analyses, a 2-tailed *P*-value <0.05 was considered significant.

TABLE 1. Demographics

	Groups	
	SCFE (n = 14)	**Control (n = 23)**
Age (y)	11.2 ± 1.4	11.3 ± 2.1
Sex (female:male)	8:6	13:10
Weight (kg)	71.55 ± 16.2	69.38 ± 15.1
Size (m)	1.55 ± 0.1	1.53 ± 0.1
BMI	29.47 ± 4.9	29.44 ± 2.7
BMI per category (n)		
Normal	0	0
Overweight	3	0
Obesity	11	23
Waist-stature index	0.58 ± 0.05	0.61 ± 0.05

Values are presented as n or mean ± SD.
BMI indicates body mass index; SCFE, slipped capital femoral epiphysis.

RESULTS

We identified 42 patients with SCFE at the time of the study; 28 were excluded, 13 for being under treatment for obesity and 15 for incomplete laboratory studies. No patients had another endocrine disease identified. A total of 37 patients were included in the study: 14 with SCFE and 23 in the control group. Demographics are provided in Table 1. Nine patients with SCFE had left involvement, 4 right, and 1 bilateral. Eleven hips were classified as stable and 3 as unstable.[18] Five cases were classified as acute evolution, and 9 as chronic. All were fixed with cannulated screws. Two patients were studied in the immediate preoperative period, and 12 in the postoperative period (mean: 9 mo, range: 0.5 to 16 mo). All patients with SCFE had high BMI: 11 with obesity and 3 with overweight (mean: 29.47; range: 23 to 37.3). All controls were obese (mean: 29.44; range: 24.67 to 35.34). In the SCFE group, 9 individuals were normotensive, and 5 had elevated BP: 2 with prehypertension and 3 with hypertension. In the control group, 9 individuals were normotensive, and 14 had elevated BP: 7 with prehypertension and 7 with hypertension (OR = 0.8, 95% CI: 0.21-33.42).

The laboratory results are summarized in Table 2. We found no significant difference when comparing children under

TABLE 2. Laboratory Results

	SCFE (n = 14)	Control (n = 23)	*P*
Glycemia (mg/dL)	85 ± 5.98	89.5 ± 9.1	0.09
Insulin (µU/mL)	26.1 ± 7.7	17.7 ± 6.6	**0.001**
HOMA	5.5 ± 1.7	3.93 ± 1.46	**0.005**
HbA1c (%)	5.3 ± 0.33	5.47 ± 0.47	0.22
Neutrophils (k/µl)	4.83 ± 1.8	4.89 ± 1.6	0.92
Triglycerides (mg/dL)	145.5 ± 68.1	107.1 ± 40.3	**0.037**
Cholesterol (mg/dL)	148.1 ± 22.3	151.7 ± 32.9	0.722
HDL (mg/dL)	36.7 ± 7.2	38 ± 9.1	0.66
VLDL (mg/dL)	34.1 ± 18.8	21.1 ± 8.2	**0.009**
LDL (mg/dL)	77.6 ± 24.8	89.5 ± 23.6	0.171

Bold indicate statistically significant *P* values.
Values are presented as mean ± SD.
P-values were calculated with *t* test for independent samples.
HbA1c indicates glycated hemoglobin; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; LDL, low-density lipoprotein; SCFE, slipped femoral capital epiphysis; VLDL, very-low-density lipoprotein.

10 years of age with older children with regard to glycemia, serum insulin, HOMA, and lipid profile. There was also no significant difference when comparing the 2 patients studied before surgery with the postoperative group. Twelve of the 13 patients in the SCFE group had high serum insulin for their age, while in the control group, 13 of 23 had high serum insulin for their age (OR = 10.0, 95% CI: 1.11-89.77). Quantitatively, the SCFE group showed a higher elevation of serum insulin (26.1 vs. 17.7 μU/mL in the control group; $P = 0.001$). HOMA was significantly higher in the SCFE group, indicating IR in 13 of the 14 cases and in 19 of the 23 controls (OR = 2.7; 95% CI: 0.27-27.35). No patient had blood glucose levels > 125 mg/dL. According to HbA1c, 3 patients with SCFE and 8 in the control group were considered at risk for T2DM, and none were diagnosed with T2DM (OR = 0.5; 95% CI: 0.11-2.5). Triglycerides increased more in the SCFE group than in the control group (mean 145.5 vs. 107.1; $P = 0.037$). Very-low-density lipoprotein (VLDL) was significantly higher in the SCFE group (34.1 vs. 21.1; $P = 0.009$). Glycemia, HbA1c, total cholesterol, high-density lipoprotein, low-density lipoprotein, and neutrophils were not significantly different between groups.

DISCUSSION

Our study showed a significant association between IR and SCFE. To our knowledge, this is the first study that associates abnormally high insulin levels with SCFE. All of our patients with SCFE had alterations in BMI for their age. To achieve a control group similar to the one studied, we recruited patients from the obesity clinic before they received treatment. Hyperinsulinemia was more prevalent in the SCFE group (OR = 10.0). Quantitatively, children with SCFE showed significantly higher levels of serum insulin and HOMA. Despite the solid relationship between SCFE and obesity, the mechanism by which obesity contributes to SCFE remains unclear, and thus obesity is usually considered a mechanical factor.[1–3] In contrast, prepubescents and adolescents have higher serum insulin levels than those younger than 7 years, more so if they are obese.[11,12] The etiology of SCFE is still not well-defined and is considered multifactorial; however, our patients often have a phenotype characteristic of obesity and signs of IR, such as acanthosis nigricans, with the hyperinsulinemia shown in this study. Considering that insulin can affect growth in the physis, particularly in the hypertrophic layer where the slip occurs,[19–21] the implications of hyperinsulinemia in the etiology of SCFE can be considerable.

Obesity is a risk factor for T2DM. Approximately 80% of patients with SCFE are obese.[3–5] To associate SCFE with the risk of T2DM, Ucpunar and colleagues compared HbA1c in patients with SCFE and obese patients of the same age. Of 51 patients with SCFE, 43 were not at risk of T2DM, 7 were at risk, and 1 was diagnosed with T2DM. In the control group, only 2 of 62 were at risk. They concluded that patients with SCFE have a significant risk of developing T2DM.[22] Although our patients showed a high prevalence of alterations in HbA1c, we found no difference between groups (OR = 0.54, $P = 0.43$). Because IR usually occurs before hyperglycemia in the course of T2DM, we believe that hyperinsulinemia and elevated HOMA are more objective parameters for defining the risk of T2DM.[16] Moreira and colleagues reported 4 cases of SCFE in one family: a father and 3 obese children aged 11, 12, and 16 years. The 3 adolescents had hyperinsulinemia, which was not directly associated with SCFE and was only attributed to obesity. The family presentation of the disease was attributed to genetic causes.[23] Hyperinsulinemia in these cases probably had a direct role in the etiology of SCFE. In contrast, obesity and hyperinsulinemia are related to diet, which is usually uniform for members of each family.

The longitudinal growth of long bones occurs through the physis, which is composed of 3 layers: rest, proliferation, and hypertrophy, each with particular features. The equilibrium between different paracrine and endocrine signaling pathways is vital for the proper functioning of the physis. Obese children and adolescents present accelerated growth earlier in the prepubescent stage, presumably due to hormonal variations.[9] In 1985, Green et al[24] suggested the theory of a dual effect between growth hormone and insulin-like growth factor 1 (IGF-1) in the physis: growth hormone acts on resting and perichondrium cells, producing cell differentiation, while IGF-1 facilitates the proliferation and hypertrophy of differentiated chondrocytes. Wang and colleagues studied the growth plate of IGF-1 null mice. They found decreased longitudinal growth despite preserving the proliferation and number of cells. The growth defect was attributed to a decrease in chondrocyte hypertrophy, which suggests an important role of IGF-1 in physis cellular hypertrophy.[25]

Insulin has also been identified as a direct stimulant of growth with effects on the differentiation and proliferation of physeal chondrocytes.[19,26,27] These effects are produced by direct stimulation of insulin receptors or by stimulation of IGF-1 production.[2,28] Wu and colleagues showed higher growth in mice with a hyperinsulinemia-producing diet. By correcting insulin levels, growth was normalized. In addition, when insulin was added to physeal chondrocyte cultures, increased proliferation and differentiation were observed. This outcome suggests a direct relationship between IR and accelerated growth.[29] In a more recent report, when comparing the tibial physis of 2 groups of mice, 1 fed a normal diet and the other fed hyperinsulinemia-producing diet, significantly higher height in the physeal plate was found in the second group. Furthermore, the height of the hypertrophic zone (dependent on the size of the hypertrophic chondrocytes) was compared between 2 other groups: one with normal mice and the other with mice in which the cartilage-specific insulin receptor gene was disrupted; the height of the hypertrophic zone was significantly lower in the latter. The same study showed that hyperinsulinemia caused activation of the insulin receptor in the physis, enough to induce skeletal growth and chondrogenesis without the apparent participation of other hormones. The authors proposed that insulin was the "principal mediator of the obesity-related accelerated statural growth and skeletal maturation in mammals, including humans."[19] Apoptosis is a crucial event in the transition from physis to bone. Hyperinsulinemia has been identified as an antiapoptotic factor in physeal chondrocytes.[19,26] This could contribute to the

broadening and eventual weakening of the physis. These effects of hyperinsulinism are consistent with findings described by Tresoldi and colleagues, who analyzed the histology of a subgroup of patients with preslip (which by definition disregards alterations caused by the mechanical effect of the slip); they found areas of normal physis alternating with zones of intense changes: thinning of the resting zone, chondrocytes grouped in hypercellular nests, and enlarged proliferative and hypertrophic zones (occupying 60% to 80% of the total physeal height), with chondrocytes grouped in clusters instead of columns. In addition, they described histochemical and ultrastructural alterations that together can contribute to reducing the mechanical resistance of the proximal femoral physis.[21] The effects of insulin found in animal and in vitro studies can be related to the histologic findings of SCFE, reinforcing the theory that physeal weakening is necessary for a slip to occur.

Our patients had a high prevalence of dyslipidemia, with triglycerides and VLDL significantly higher in the SCFE group. The association of IR with this combination of abnormalities (high triglycerides and VLDL, low high-density lipoprotein and normal low-density lipoprotein) is known as diabetic dyslipidemia. Cardiometabolic risk factors, defined by the American Academy of Pediatrics, include triglycerides > 110 mg/dL.[30] The average triglycerides were clearly higher in the SCFE group (145.5 mg/dL) and slightly lower in the control group (107.1 mg/dL). Arterial hypertension has also been associated with skeletal diseases typical of adolescents with obesity, such as tibia vara and SCFE. This outcome suggests more intense metabolic abnormalities or of a different nature in patients with growth plate diseases.[13] Our patients have increased cardiometabolic risk, which makes them more likely to develop hypertension. Although 51% of our patients had alterations in BP, unlike what was found by Taussig and colleagues, our study showed no significant difference between groups (OR = 0.8).

The association among obesity, hyperinsulinemia, and SCFE is obvious in our study. The known effects of insulin on growth cartilage may explain the physeal mechanical insufficiency to support the abnormally high or repetitive loads in accelerated growth stages that lead to SCFE. However, there is a lack of studies that demonstrate these alterations directly in the physeal plates of individuals with hyperinsulinemia. The prevalence of diabetes and obesity in our environment is very high. We do not know whether our results are reproducible in other ethnic groups. This study has limitations. Although the recruitment of patients was consecutive and without apparent selection bias, we had difficulty completing the laboratory analysis of all patients with SCFE at the time of the study, which resulted in a small sample, and we do not know whether our findings apply to excluded patients. Patients in the control group were asymptomatic, but we did not take x-rays to rule out subclinical SCFE. The role of diet in IR and the metabolic profile was not analyzed. Family history was not studied for T2DM and IR.

In conclusion, abnormally high serum insulin levels were significantly associated with SCFE with likely strong etiological implications. SCFE patients consistently showed elevated levels of insulin, HOMA, triglycerides, and VLDL, even higher than the group of children with obesity. Clinical suspicion, family environment, genetic burden for T2DM, obesity, and the so-called diabetic dyslipidemia should alert clinicians to the risk of IR and T2DM. On the basis of this finding, strategies can be developed to detect patients at risk for SCFE in a timely manner. We suggest orthopaedic evaluation, complemented with radiographic studies at the discretion of the evaluating physician, for all children with obesity and IR.

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